REMARKS

This is in response to the Office Action dated January 2, 1985 for the above-identified application. The specification has been amended to correct typographical errors. The claims have been amended in view of the Examiner's remarks.

The Examiner entered a restriction requirement, requiring election of claims 1-4 and 16-31 or claims 5-7. Applicant hereby confirms the provisional election of claims 1-4 and 16-31 made by telephone.

The present invention encompasses the base addition salts of omeprazole, pharmaceutical preparations containing these salts, and a method of treating gastric disorders using these salts. The base addition salts provide surprisingly improved stability relative to neutral omeprazole, and are therefore substantially superior where storage and subsequent distribution are contemplated.

The Examiner rejected claims 1-4 and 16-31 under 35 U.S.C. §103 as obvious over Senn-Bilfinger, European Patent Applications Nos. 5129 and 45200 and Elderfield, all taken together. EPA 5,129 and EPA 45,200 disclose omeprazole in its neutral form. Elderfield discloses that the -NH- group of unsubstituted benzimidazole can act as either a base or an acid. Senn-Bilfinger discloses a compound which is allegedly structurally similar to omeprazole, having a $-CF_3$ substituent rather than $-OCH_3$, and base addition salts thereof. Based on these references, the Examiner alleges that the base addition salts of omeprazole are obvious. Applicant respectfully disagrees.

As noted above, the base addition salt of omeprazole is surprisingly more stable than neutral omeprazole. Evidence of this increase in stability is given in the specification on pages

13-14. The test data show that neutral omeprazole undergoes fifteen times more degration than the sodium salt over a six-month period. Nothing in the cited references suggests this surprising improved stability.

Further, applicants submit that the comparison of omeprazole salts with salts of the trifluoromethyl derivative of Senn-Bilfinger and the unsubstituted benzimidazole of Elderfield is not chemically meaningful. Changes in substituent groups can produce dramatic effects in the acidity of the -NH- group in the benzimidazole moiety. In view of the differences between the trifluoromethyl derivative and omeprazole, applicant submits that the cited references do not suggest that base addition salts of omeprazole could be made, or that if made would have improved stability.

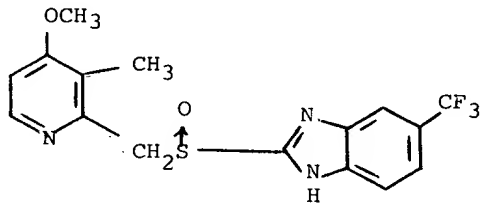
Elderfield discloses that unsubstituted benzimidazole is acidic. This is not dispositive, however, of the acidity of substituted benzimidazole. Benzimidazole itself is acidic due to resonance stabilization of the resulting anion. This means that substituents added to the benzimidazole can have pronounced effects on the acidity, depending on whether they stabilize or destabilize the anion. This effect is pointed out in the attached page 831 from Organic Chemistry, 3d Ed. by Morrison and Boyd which catalogs the stabilizing and destabilizing effects of substituents on resonance stabilized anions.

Comparing the substituted benzimidazole of Senn-Bilfinger and omeprazole, the only difference is the single substituent group $-CF_3$ versus $-OCH_3$. This difference is substantial, however, since $-CF_3$ will act strongly as an electron withdrawing group and will stabilize the anion, while $-OCH_3$ will destabilize the anion. Thus, the compound of Senn-Bilfinger would be expected to be substantially more acidic than omeprazole.

In this light, applicant notes that in the preparation of the basic salt of the trifluoromethyl derivative, Senn-Bilfinger used sodium hydride, a very strong base. This suggests that even with the stabilizing effect of the $-CF_3$ group, these benzimidazole derivatives are not strong acids. Since omeprazole should be much weaker acid than the trifluoromethyl derivative, Senn-Bilfinger provides no suggestion to one skilled in the art that base addition salts of omeprazole could be made at all.

In further support of the unobviousness of the base addition salts of omeprazole, applicants have conducted tests on sodium omeprazole and the sodium salt of the trifluoromethyl derivative. These tests show that not only are base addition salts of omeprazole surprisingly more stable than neutral omeprazole, they are also more stable than the 5-trifluoromethyl-2-[(4-methoxy-3-methyl-2-pyridinylmethyl)-Sulfinyl]-(1H)-benzimidazole sodium salt prepared in accordance with Example 18 of Senn-Bilfinger. The neutral compound is described in Example 3 of Senn-Bilfinger.

The stability in solution of sodium omeprazole and the sodium salt of



a trifluoromethyl derivative which is disclosed in Example 3 of Senn-Bilfinger, were compared. The two sodium salts were dissolved in buffer solution. The pH of the final solutions was 9.02.

The solutions were stored at 37°C and samples were periodically taken. The samples were analyzed by HPLC to determine the content of undegraded substance. The decrease in

the concentration of the test substance with time was used to calculate a first order rate constant and a half-life for each substance. The rate constants thus obtained are as follows:

Test Substance	Rate Constant (min^{-1})	$t_{1/2}$ (hr)
omeprazole, sodium salt	$8.19 \pm 0.08 \times 10^{-5}$	141
trifluoromethyl derivative, sodium salt	$2.21 \pm 0.02 \times 10^{-3}$	5.2

These test results clearly show that sodium omeprazole is many times more stable than sodium salts of the trifluoromethyl derivatives disclosed by Senn-Bilfinger. Accordingly, sodium omeprazole is much more suitable for use in intravenous applications where stability in aqueous solution is of critical importance. The standard for solutions for injection to be of acceptable quality is not more than 1% degradation of the active substance. Applying this standard to the two substances tested, 2.05 hours will be available for administration of sodium omeprazole following preparation of the solution. On the other hand, solutions of the trifluoromethyl derivative will be useable for only 4.5 minutes following preparation.

Applicants have also tested the magnesium and calcium salts of omeprazole, and these demonstrate the same surprising improvement in solid state stability relative to neutral omeprazole that was described for the sodium salt in the specification.

Samples of neutral omeprazole; and of the sodium, magnesium and calcium salts of omeprazole prepared according to the present application, were placed in amber glass bottles with snap-cap polyethylene closures and stored at 50°C. A second set of samples were placed in open petri dishes and stored at 37°C

and 80% relative humidity. At various times, samples were removed and analyzed by HPLC for the total amount of degradation products.

The results of the degradation studies are as follows:

Table

Total amount of by-products found after storage of omeprazole and omeprazole salts. The results are given as percent of intact omeprazole (peak area percent)

Storage time, months	Storage conditions °C/% r.h.	Omeprazole	Omeprazole sodium salt	Omeprazole magnesium salt	Omeprazole calcium salt
0	-	0.2	0.1	0.2	0.2
1*	+50	0.2			
	+37/80	0.2	0.1	0.3	1.5
3	+50	1.0	0.1	0.4	0.9
	+37/80	0.3	0.8	0.4	1.7
6	+50	>4	0.1	0.6	1.1
	+37/80	>6	1.2	0.7	1.7

*The magnesium and calcium salts were analysed after 1.5 months storage.

It is obvious from these results that all of the base addition salts tested display substantially enhanced long-term stability relative to neutral omeprazole. This improved stability is highly significant for the successful marketing of a pharmaceutical formulation.

The Examiner rejected claims 16-19 under 35 U.S.C. §112. Claims 16-19 have been amended to recite an intended use, an effecive amount of the active ingredient and a pharmaceutical carrier.

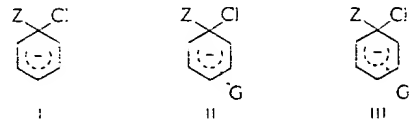
Based on the remarks hereinabove and the amendments, applicants submit that claims 1-4 and 16-31 are unobvious and in condition for allowance. Favorable reconsideration and allowance of the claims are respectfully requested.

Respectfully submitted,

Allan H. Bonnell

Allan H. Bonnell
Patent Office Reg. No. 22,059

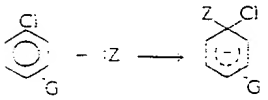
Attorney for Applicant
(212) 408-2500



I II III

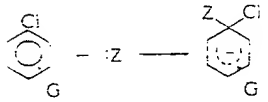
A group that withdraws electrons (II) tends to neutralize the negative charge of the ring and so to become more negative itself: this dispersal of the charge stabilizes the carbanion. In the same way, electron withdrawal stabilizes the transition state with its developing negative charge, and thus speeds up reaction. A group that releases electrons (III) tends to intensify the negative charge, destabilizes the carbanion (and the transition state), and thus slows down reaction.

Nucleophilic Aromatic Substitution



G withdraws electrons: stabilizes carbanion, activates

G = $-N(CH_3)_3^+$, $-NO_2$, $-CN$, $-SO_3H$, $-COOH$, $-CHO$, $-COR$, $-X$



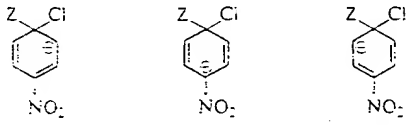
G releases electrons: destabilizes carbanion, deactivates

G = $-NH_2$, $-OH$, $-OR$, $-R$

It is clear, then, why a given substituent group affects nucleophilic and electrophilic aromatic substitution in opposite ways: it affects the stability of negatively and positively charged ions in opposite ways.

25.10 Orientation in nucleophilic aromatic substitution

To see why it is that a group activates the positions *ortho* and *para* to it most strongly, let us compare, for example, the carbanions formed from *p*-chloronitrobenzene and *m*-chloronitrobenzene. Each of these is a hybrid of three structures, I–III for *para* attack, IV–VI for *meta* attack. In one of these six structures, II,



Para attack

I II III

Especially stable: charge on carbon bearing substituent